September 9, 1998

This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical and it is presented here exactly as submitted.

October 19, 1997

Ms. Kylie Rothwell
Chemical Review Manager
Special Review and Reregistration Division
Office of pesticide Programs H7504C
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, DC 20460

SUBJECT: profenofos; Response to Draft RED chapters from HED (6/18/96) and EFED (6/17/96). (Case 2540; Chemical 111401)

Dear Ms. Rothwell,

Novartis appreciates the opportunity to respond to the draft Reregistration Eligibility Decision chapters from HED and EFED. The comments in this letter will address primarily the areas of toxicology, worker exposure and ecological assessment. Novartis is not including, at this time, any risk assessments for dietary or drinking water exposure. The Agency did not have a concern with its dietary risk assessment and did not supply the details for Novartis to consider. The following discussions were jointly prepared with Novartis associates Dr. Linda Meyer, Mr. Frank Selman, and Dr. Jonathan Akins.

HED - Human Health Assessment

The draft RED chapter from HED, while comprehensive, contains some inaccuracies. Novartis requests that the Agency consider changes to the toxicology profile as discussed below. In the RED table summarizing acute toxicity values for profenofos technical, a more recent acceptable dermal LD50 study in the rabbit is available and should be used in place of the 1982 study (MRID 00109427) cited. Study No. 5522-88 (MRID 42021501) was conducted in 1988 and was submitted to meet commitments made in Phase 3 of FIFRA 88 Accelerated Reregistration for profenofos (Case No. 2540). The dermal LD50 values established in this study were 2450 mg/kg for males, 2790 mg/kg for females and 2560 mg/kg for males and females combined. These results place profenofos in Toxicity Category III for dermal toxicity.

Also in RED Table 2, results of the acute delayed neurotoxicity study in the hen (MRID 00126485) need to be corrected. The no observed effects level (NOEL), cited as 52 mg/kg (20 mg a.i./kg), has been corrected twice for purity of the formulation used. The NOEL should be cited as 117 mg/kg (52 mg a.i./kg). Similarly, the dose level at which 100% mortality occurred is incorrect and should read 234 mg/kg (104 mg a.i./kg). The results cited for the LD50 value (127 mg/kg (56.3 mg a.i./kg) are correct as is. This study is also discussed in Section i. (3) Acute

Delayed Neurotoxicity Study on page 10 and clarification should be made for dose levels representing mg a.i./kg there, as well.

Novartis believes the results cited for the acute oral neurotoxicity study in the rat should indicate that there was no histopathological evidence of neurotoxicity at any dose level. Additionally, the results observed at the 190 mg/kg dose level are overstated. Treatment-related effects at 190 mg/kg were limited to an increased incidence of compulsive licking in males and increased incidences of staining of the nose in males and females. The statement that multiple effects were seen in each sex at this dose level hardly seems to accurately represent these limited findings.

The more detailed discussion of study findings in Section i. (Acute Neurotoxicity Study) indicates that at 190 mg/kg, males showed an increased incidence of staining of the nose and compulsive licking (stereotypy). We agree with this statement. Females are said to have exhibited an increased incidence of diarrhea, miosis, staining of the nose, abnormal gait and increased ease of handling. Only 1/10 females at 190 mg/kg demonstrated diarrhea. While 6/10 females at 190 mg/kg demonstrated miosis, 5/10 controls demonstrated miosis at this time point and at pretest 6/10 controls demonstrated miosis. Only 1/10 females demonstrated hunched gait. While 10/10 females at 190 mg/kg were ranked as easy to handle during the time of peak effect versus 6/10 controls, these incidences are exactly the same as were reported during the pretest time period for these dose groups. Therefore, none of these findings can be considered to be related to treatment with profenofos. The only treatment-related finding in females at 190 mg/kg is an increased incidence of staining of the nose. Rather than indicating that the lowest observed effects level (LOEL) for neurotoxicity was 190 mg/kg based on multiple effects in each sex, a more appropriate conclusion or summary statement of results observed at this dose would be "The LOEL of 190 mg/kg was based on increased incidences of compulsive licking in males and staining of the nose in males and females".

Novartis agrees that the non-guideline two-phase acute oral toxicity study cited in Section c. Toxicological Endpoints on page 12 is the appropriate basis for characterizing acute dietary risk. However, Novartis does not agree with several of the NOELs for various endpoints cited on pages 12 and 13. Specifically, the NOEL for plasma cholinesterase activity inhibition in female rats is cited as 0.1 mg/kg. However, mean plasma cholinesterase activity for females at 0.5 mg/kg is not statistically different from controls and is, in fact, not different from the mean for females in the 0.1 mg/kg group. The NOEL for plasma cholinesterase activity inhibition is 0.5 mg/kg for females, as well as males. Further, the NOEL for inhibition of brain cholinesterase activity in both males and females is cited as 25 mg/kg. Mean brain cholinesterase activity for males and females at 100 mg/kg is not significantly different than controls (97% and 86% of control values for males and females, respectively). The NOEL for brain cholinesterase inhibition is 100 mg/kg for both male and female rats.

HED - Occupational Exposure

EPA estimated the dermal and inhalation exposure to mixers, loaders, applicators or other handlers using default use-patterns rather than specific use data associated with profenofos. Because chemical-specific handler exposure data have not been generated, surrogate data was

used from PHED V1.1 for the assessment. The OREB assessment estimates are based on upper-bound acreage that may be treated in a single day. For aerial applications, OREB used 800 acres as the maximum daily acres treated. This estimate is rarely used by HED in its draft RED chapters but is sometimes used for cotton, and is expected to be possible only under absolutely perfect weather conditions. Novartis respectfully submits that use of 800 A/day is not representative of normal use patterns, since the possibility of a pilot treating 800 acres/day and using profenofos on all 800 acres in that day is extremely remote. For aerial applications a more representative estimate of 350 A/day should be used to assess worker exposure.

Novartis believes that the greatest issue regarding the profenofos RED risk assessment is the NOEL used in the risk assessment. The NOEL used for assessing short-term and intermediate-term occupational risk is 1.0 mg/kg/day obtained from the 21-day dermal toxicity study. The LOEL is 10 mg/kg/day, based on cholinesterase inhibition. The 10 fold difference between the NOEL and the LOEL must be resolved. Novartis is considering conducting a study to resolve this difference between the NOEL and LOEL. Novartis is also evaluating changing Curacron 8E packaging to a closed system for mixing/loading. These two changes will effectively increase MOEs to acceptable levels for mixer/loader-applicators, hoers, and scouts. Novartis also respectfully submits that although the Agency has calculated MOEs less than 100 (based on default numbers), EPA also has commented in the draft RED that occupational safety of profenofos has been demonstrated by the paucity of reported poisoning incidences.

EFED - Ecological Assessment

The ecological risk assessment within the profenofos RED utilized the standard EPA risk quotient method which provides an easy and conservative mechanism to regulate risk of pesticide use to non-target organisms (EPA, 1986; EPA, 1994). The Agency concluded that profenofos poses high risk to the environment with risk quotients exceeding levels of concerns for birds, mammals, insects, and aquatic organisms for both endangered and non-endangered species. Furthermore, the Agency indicated that two additional chronic toxicity tests (chronic marine and fish full life cycle toxicity tests) will be requested to better assess the chronic risk associated with profenofos use.

Novartis partially concurs with the Agency's prediction that, under the conservative risk quotient assumptions, profenofos could pose high risk to nontarget aquatic but not terrestrial organisms. While the risk quotient method provides an easy and conservative mechanism to regulate risk, it is especially conservative in the exposure estimation for terrestrial organisms. The terrestrial exposure estimation assumes avian and mammalian species exclusively eat short grass directly from the treated field, which undoubtedly is not the case for the species associated with cotton.

In response to the Agency's RED, Novartis proposes mitigation methods to prevent nontarget aquatic organism's exposure and risk:

) Drift management language will be strengthened;
) Buffer strips will be required for both ground and aerial application;

) Education programs will continue regarding the proper use of cotton insecticides to prevent adverse impacts on nontarget terrestrial and aquatic organisms.

Nontarget Terrestrial Organism Exposure and Risk Assessment

The Agency has utilized the maximum Kenega value on short grass immediately after application (240 ppm on day 0) as the estimate of exposure towards the calculation of terrestrial organisms' acute and chronic risk (Hoerger and Kenega,1972). By utilizing the most conservative exposure estimate, the Agency indicated that profenofos poses high acute and chronic risk to avian species. However, additional information defining terrestrial organism's exposure and risk indicates that risk to terrestrial species is minimal, since:
) The amount of short grass in the application target area is minimal;
) Most birds utilize habitats adjacent to but not in cotton fields;
) The diets of birds associated with cotton cultivation consist primarily of insects and seeds and not short grass.

Cotton is a high value crop that is highly managed with herbicides. Traditionally, monocots (grass) and dicots (weeds) are aggressively managed with both pre- and post-planting applications of herbicides, and the density of grass and weeds within cotton cultivation is minimal. Cotton fields provide poor foraging grounds and cover for grazing species, granivores and insectivores. The vast majority of avian species associated with cotton fields, therefore, breed and forage in adjacent habitats. In a recent paper conducted for Novartis (Tank and Brewer, 1997), an avian census in cotton in Louisiana indicated that avian use of cotton fields is minimal compared to edge habitats. In this study, 732 birds from 17 species were observed in the habitat edges adjacent to the cotton fields while only 33 birds of 7 species were observed within the crop. Therefore, the vast majority of birds and avian forage items will not be directly exposed to the profenofos applications but to a small fraction of the application as drift.

In the 1997 report, the majority of birds associated with cotton were songbirds, but other species included shorebirds and upland game birds. During the season when profenofos applications are made, songbird and gamebird diets primarily consist of invertebrates and weed seeds but not short grass (Martin et al. 1951; Terres, 1991). The only avian species whose diet primarily consists of grass are waterfowl, which are not associated with cotton cultivation. It should be emphasized that birds associated with cotton are not grazers, and primarily consume weed seeds and insects. Any exposure modeling for avian species associated with cotton cultivation should assess the exposure according to their specific diets. It is therefore the opinion of Novartis that the appropriate exposure scenario for Tier one avian assessment should utilize the insects and weed seeds as the avian forage items.

Acknowledging the dietary importance of insects and seeds for birds during the breeding season, Novartis conducted a profenofos/cotton field study designed to measure profenofos residues on insects and seeds following the maximum use rate of profenofos (Tank and Brewer et al., 1997). Profenofos (1 lb a.i./A) was applied to cotton fields containing insects and millet seeds housed in enclosures. Millet seeds and insects were sampled on application days -1, 0, 1, 3, 7 and 14 from

both the application site and adjacent to the cotton fields. The greatest mean profenofos residues on insects were found on day 1 post application at 0.11 ppm (moths), day 3 at 1.8 ppm (crickets), day 4 at 0.21 ppm (beet armyworm larvae), day 0 at 0.51 (mealworm) ppm. The greatest mean residues on millet seed occurred on day 0 at 4.60 ppm. The field study residue values for the insects and seed are considerably less than the Kenega Nomogram prediction for small insect (58 ppm), large insects (10-12 ppm) and seeds (10 ppm). The differences in the modeled and actual results are not unexpected since the data collected to create the Kenega Nomogram did not actually include insects or seeds; pesticide residues on insects were assumed to have similar residue levels as forage crops and pods containing seeds.

Since there is little to no short grass located in the target application area and since grazing species do not utilize cotton cultivation, a more realistic calculation of terrestrial risk indicates minimal risk to avian species. The Novartis field study showed that the terrestrial forage items contained significantly less profenofos residue than the Kenega Nomogram predicted and that profenofos poses minimal acute and chronic risk to birds.

While the Agency's ecological risk assessment indicates profenofos poses high risk to birds and mammals, there have been, to our knowledge, no terrestrial wildlife die-offs associated with profenofos use on cotton over the full 15 years of its registration. A similar opinion was formed in the U.S. Department of the Interior document "Toxicology and Pesticide Use in Relation to Wildlife: Organophosphorous and Carbamate Compounds" where the author states:

"There are no published reports relating the use of profenofos to wildlife die-offs. The relatively low number of acres treated with profenofos may minimize wildlife exposure to this chemical." (Smith, 1992).

We agree that the relatively low number of acres treated with profenofos would decrease the potential for wildlife die-offs, but it is our opinion that more pertinent reasons for the lack of wildlife mortality incidences are based on wildlife habitat selection and foraging behaviors.

Nontarget Aquatic Organism Exposure and Risk Assessment

The Agency estimated that drift and run-off would result in aquatic profenofos concentrations of 5.96, 2.6, 1.1, 0.75 ppb on post-application days 0, 4, 21, and 56, respectively. According to the Agency, 84% of profenofos was transported as drift to the theoretical farm pond, 15% dissolved in runoff water, and 1% adsorbed to particles in runoff. Using this conservative estimate of exposure, the Agency concluded that profenofos poses high risk to the environment with risk quotients exceeding levels of concerns for aquatic organisms. Furthermore, the Agency indicated that a chronic marine and fish full life cycle toxicity test will be requested to better assess the chronic risk associated with profenofos use.

To address these issues, educational programs were initiated by Novartis and the Cotton Council to educate end-product users. The education program emphasizes proper application timing and drift management to avoid adverse impacts to nontarget areas. Overall, these educational

programs have been extremely successful; no profenofos 6(a)2's have been reported following the educational programs in Mississippi and Louisiana which were sites of the most recent of the die-off events. In Mississippi, the educational program was also adopted by the state as part of its certifying process for applicators and handlers. The educational program will be expanded to Alabama, Arizona, Georgia, Texas, and all cotton belt states.

While the current label states "do not apply within 300 feet upwind of impounded water", Novartis proposes to change the label to require buffer strips for both ground (100 feet) and aerial (300 feet) applications regardless of wind direction, providing less opportunity for human judgment error. Furthermore, details on application timing and methods will be expanded on future labels to decrease the potential for profenofos to drift or run-off into nearby waterways.

Request to Reconsider the Need for Additional Chronic Aquatic Testing

As far as the proposed request for additional chronic toxicity tests (chronic marine invertebrate and fish full life cycle tests), Novartis requests the Agency reconsider the need for additional chronic aquatic testing based on the educational programs, buffer strips, existing chronic aquatic data, bridging studies from previous studies conducted with acetylcholinesterase inhibitors, and existing data that indicates rapid degradation of the active ingredient.

First, Novartis will decrease the exposure of aquatic organisms to negligible and safe levels through applicator/handler training programs and label changes. Both actions are designed to decrease the possibility of profenofos to drift or run-off into adjacent waterways. Second, chronic invertebrate and fish studies have been previously conducted with profenofos: chronic daphnia, chronic mysid (unsubmitted) and fish early life stage. In the acute invertebrate studies, daphnia was more sensitive than any of the marine invertebrates to profenofos and was a logical species for higher tiered/chronic testing. Additionally, results from the daphnia chronic (NOEC = 0.2 ppb) and the mysid chronic (NOEC = 0.22 ppb) studies were nearly identical. Third, profenofos is an organophosphate that has a similar mode of action as all organophosphates and carbamates, causing acetylcholinesterase inhibition. The physiological and behavioral responses of animals exposed to acetylcholinesterase inhibitors have been well established in the scientific literature. Considering the similar mode of action with other acetylcholinesterase inhibitors and the existing fish early life stage test, we will be able to predict the results of a fish full life cycle study with profenofos through comparison with other previously tested acetylcholinesterase inhibitors (chlorpyrifos, carbaryl, methomyl, etc.). Finally, rapid aerobic soil metabolism (1.9 days), hydrolysis (7.2 hour @ pH 9 and 62 days @ pH 7), anaerobic soil metabolism (2.9 days), and anaerobic aquatic metabolism (3.2 days), is predicted to degrade profenofos rapidly on land and in water, decreasing the potential for significant chronic aquatic exposure. The duration of a fish full life cycle is approximately 300 days.

Conclusion

In conclusion, Novartis requests that the Agency make changes to the toxicology profile of

profenofos as indicated in the first section of this response.

For worker exposure, it can be shown that a modest increase in the 21-day dermal NOEL can resolve risk concerns. There appears to be ample room to improve this NOEL, as the LOEL is an order of magnitude greater. Novartis is considering conducting a new 21-day dermal toxicity study that would potentially provide better resolution of the NOEL than is currently available.

Novartis partially concurs with the Agency's prediction that, under the conservative risk quotient assumptions, profenofos could pose high risk to nontarget aquatic but not terrestrial organisms. Novartis proposes that drift management language be strengthened, buffer strips be required for both ground and aerial application, and education programs continue regarding the proper use of cotton insecticides to prevent potential adverse impacts on nontarget terrestrial and aquatic organisms. These actions will ensure risk to aquatic organisms remains at negligible levels, and additional chronic aquatic toxicity testing will not be necessary.

Finally, Novartis is proud of its educational and stewardship programs that are in place for profenofos. Enclosed with this letter is a copy of the materials for the "Careful by Nature" program. It is evident from the decline in environmental incidents and 6(a)2 reports over the last two years that these efforts are increasing the safety of this product. Novartis is also participating in the launch of a new safety education/awareness program called the "Safety: Apply It First". This program begins on Nov. 1, 1997 and is sponsored by Novartis and 7 other agricultural chemical companies. It delivers important safety information and encourages good stewardship practices to handlers of organophosphate and carbamate pesticides. The program is being introduced nationally through advertising in major trade journals, radio public service announcements, direct mailings and during presentations made at sales meetings, dealer grower meetings and at pesticide applicator training schools.

Thank you for allowing Novartis to review these chapters of the RED before they are finalized. If you have any questions regarding this response, please contact me at (910) 632-2391.

Sincerely,

Robert E.M. Wurz, Ph.D.
Senior Regulatory Manager
Regulatory Affairs

References

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Enclosures

"Careful by Nature" Stewardship Program